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(54) Title: ENHANCED TRANSDERMAL TRANSPORT USING ULTRASOUND

(57) Abstract

Several means for enhancing transdermal transport of drugs and analytes have been developed, including the use of low frequence ultrasound, chemical modifiers of permeability and/or cavitation, iontophoresis and/or electroporation (electric fields), pressure and/or vacuum (physical enhancers), and magnetic force fields. Applications of low-frequency (approximately 20 KHz to 1 MHz) ultrasound enhances transdermal transport of drugs and measurements of the concentration of analytes in body fluids such as blood or lymph. Delivery can be further enhanced or controlled through the use of carriers for the drugs, such as liposomes or microparticles, using a wide range of ultrasound frequency ranges and intensities. The microparticles are preferably small, and may have surfaces with increased hydrophilicity or lipophilicity to further enhance transport.

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AMENDED CLAIMS
[received by the International Bureau on 6 March 1997 (06.03.97);
original claims 1-24 replaced by amended claims 1-24 (3 pages)]

1. A use of an apparatus for enhancing transport of molecules across the skin comprising means for applying ultrasound to the skin, wherein the ultrasound is application at a frequency of between 20 kHz and less than 1 MHz for a period of time effective to transport the molecules through the skin.

2. The use of claim 1 wherein the molecules are drugs to be administered to a person in need thereof.

3. The use of claim 1 wherein the molecules are analytes present in blood, lymph or interstitial fluid.

4. The use of claim 1 wherein the frequency is between 20 and 45 kHz.

5. The use of claim 1 wherein the intensity is between zero and 1 W/cm^2.

6. The use of claim 5 wherein the intensity is between 12.5 mW/cm^2 and 225 mW/cm^2.

7. A method of using the apparatus of any of claims 1-6 to enhance transfer of molecules through the skin by applying ultrasound at a frequency of between 20 kHz and less than 1 MHz for a period of time effective to transport the molecules through the skin.

8. A method for extracting an analyte to be measured in a blood or body fluid sample comprising applying at an appropriate site for extraction of a sample an effective amount of ultrasound and collecting the extracted sample, wherein the ultrasound is applied at a frequency between 20 kHz and less than 10 MHz.

9. The method of claim 8 wherein the ultrasound is applied at a frequency of between 20 kH and less than 1 MHz.

10. An apparatus for enhancing transdermal transport of molecules comprising means for administering to the skin an effective amount of ultrasound for transdermal transport of molecules in combination with an enhancer selected from the group consisting of chemical enhancer combinations of agents enhancing solubility of the molecules to be transported with agents enhancing the fluidity of lipid

bilayers, mechanical force fields, osmotic force fields, magnetic force fields and electric force fields.

11. The apparatus of claim 9 wherein the ultrasound is administered at a frequency of less than 2.5 MHz.

12. The apparatus of claim 9 wherein the ultrasound is administered at a frequency of 1 MHz or less.

13. The apparatus of claim 9 wherein the combination is linoleic acid in an ethanol solution.

14. The apparatus of claim 9 wherein the ultrasound is administered in combination with an electric force field selected from the group consisting of electroporation and iontophoresis.

15. The apparatus of claim 13 wherein the electric field is pulsed.

16. The apparatus of claim 9 wherein the ultrasound is administered in combination with a magnetic force field.

17. The apparatus of claim 9 wherein the ultrasound is administered in combination with a mechanical force field created by pressure or vacuum.

18. The apparatus of claim 9 wherein the ultrasound is administered in combination with an osmotic force field.

19. The apparatus of claim 9 wherein the ultrasound is administered in combination with chemical enhancers and mechanical forces.

20. The apparatus of claim 1 wherein the molecules to be transported are drugs the patient is in need of.

21. The apparatus of claim 9 wherein the compound to be transported is an analyte to be measured.

22. The apparatus of claim 9 wherein the ultrasound is pulsed.

23. The method of use of the apparatus of any of claims 9-21 in enhancing transport of molecules through the skin.

22. A composition for enhancing delivery of drugs across the skin comprising drug encapsulated in a liposome or polymeric carrier for application to the skin and applying ultrasound for a period of time effective to deli

23. The composition of claim 22 wherein the microparticle is coated with a lipophilic or hydrophilic material enhancing transdermal penetration.

24. The composition of claim 22 wherein the material is a hydrophilic molecule couple to a synthetic biodegradable polymer forming the microparticle.